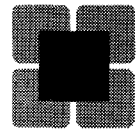

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Thrombolytic therapy

A review (Part 1 of 2)

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■ Despite the discovery of thrombolytic agents more than 50 years ago, only recently has major interest become evident in their use to treat myocardial infarction, venous thromboembolism, and peripheral arterial disease. Use of thrombolytic drugs may result in myocardial and limb salvage as well as improved survival rates and quality of life for patients affected by potentially devastating vascular disease. We review historical highlights, outstanding studies, and important aspects of thrombolytic therapy, emphasizing its use in peripheral vascular disease.

□ INDEX TERM: FIBRINOLYTIC AGENTS □ CLEVE CLIN J MED 1989; 56:189–196

IN 1933, Tillet and Garner[1] showed that sterile filtrates from beta-hemolytic strains of streptococcus from human infections could liquify fibrin clots. Furthermore, the authors noted that clotted blood from individuals who had recently recovered from streptococcal infection was often highly resistant to dissolution by this same filtrate and that serum from these individuals could prevent fibrinolysis of normal clot by the streptococcal filtrate. Milstone[2] proposed that a lytic factor in human blood enables bacterial filtrate to lyse clots. Christensen[3] reported in 1945 that fibrinolysis of clots occurred after a zymogen, "lysin factor" (now known as plasminogen) is converted to an active proteolytic enzyme (i.e., plasmin). Spontaneous activation could occur, but additional streptococcal fibrinolysin (later named streptokinase) caused rapid clot dissolution. A separate plasminogen activator present in animal tissue cells was proposed by Fischer[4] in 1946 and is now called tissue plasminogen activator (t-PA). A third plasminogen-activating kinase, urokinase, was found in 1947 by MacFarlane and Pillig[5] upon noting fibrinolytic activity of urine.

Fibrinolysis has been recognized for more than 200 years and has been studied for the past 50 years. A recent surge of interest in fibrinolytic therapy for acute myocardial infarction and peripheral vascular disease reflects in part:

1. Improved endpoints of efficacy (e.g., safe angiographic techniques, particularly important in critically ill patients).
2. Increased appreciation of the role of thrombosis (i.e., in vascular occlusion and in subsequent tissue damage) and increased understanding of reperfusion in salvage of jeopardized vascular tissues.
3. Synthesis of key activators of the fibrinolytic system in commercial quantities.

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FIBRINOLYTIC SYSTEM

Plasminogen, formerly called "lysin factor," is a single-chain glycopeptide zymogen synthesized in the liver. Hydrolysis of the Arg-Val (560–561) peptide bond activates this precursor, forming the fibrinolytic enzyme,

plasmin.[6] This mode of activation occurs via intrinsic or humoral activators (e.g., Factor XII, kininogen, prekallikrein), extrinsic activators (e.g., t-PA, urokinase), or via exogenous activators (e.g., urokinase, streptokinase).[7]

Plasmin is a two-chain polypeptide linked by a disulfide bond.[8] As a nonspecific serine protease, it is capable of degrading fibrin as well as fibrinogen and coagulation factors V, VIII, and XIII.[9] Plasmin binds to fibrin via its lysine binding site. This fibrin-bound plasmin has a long half-life (approximately 10 seconds) and acts to degrade the fibrin polymers to fibrin degradation products. Fibrinogen and noncrosslinked fibrin also act as substrate to plasmin and are broken down into specific degradation products.[10]

Freely circulating plasmin is quickly inactivated by antiplasmins.[11] By attaching at the lysine binding site, alpha-2 antiplasmin forms a 1:1 inactive complex with freely circulating plasmin.[12] If alpha-2 antiplasmin becomes depleted, a slower inhibitor—alpha-2 macroglobulin—may replace it. Exogenous activators of plasmin may overwhelm both antiplasmins, resulting in rapid systemic degradation and depletion of fibrinogen.[13] Plasminogen can be inactivated pharmacologically by a lysin analog (i.e., epsilon amino-caproic acid) that binds at the lysine binding site, inhibiting plasminogen from binding to fibrin.[14]

THROMBOLYTIC AGENTS

Large clinical trials of t-PA in the treatment of acute myocardial infarction, peripheral artery disease, venous thrombosis, and pulmonary embolism have recently been undertaken. T-PA has not only engendered renewed interest in thrombolysis, these new trials have sparked further research into the thrombolytic activities of urokinase and streptokinase.

Streptokinase

Streptokinase, the first thrombolytic agent discovered, was until recently the most widely used such agent. A nonenzyme protein, it forms a 1:1 bond with plasminogen, creating an activation complex that hydrolyzes uncomplexed plasminogen to plasmin [15] (*Figure 1*). Isolated from Group C beta-hemolytic streptococci, streptokinase has a half-life of 16–18 minutes in the presence of antibodies and 83 minutes when antibodies are absent. Its efficacy has been well documented, and it is the least costly thrombolytic agent.

Fibrin specificity or affinity is low, resulting in a systemic lytic state of fibrinogen depletion and potential hemorrhagic hazards. The risk of bleeding does not appear to be related to the streptokinase dose[16] but may be related to lack of clot selectivity, existence of prior hemostatic defects, or duration of infusion. The overall risk of significant bleeding may depend on the indication and regimen used. The antigenic properties of streptokinase often cause fever and rash; bronchospasm, angioneurotic edema, and hypotension result less frequently.[16]

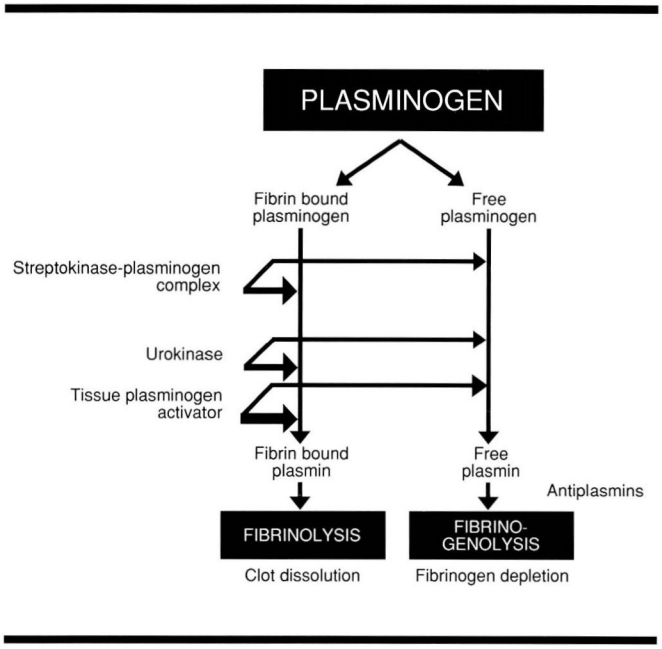

FIGURE 1. The effect of streptokinase, urokinase, and t-PA on fibrin-bound plasminogen and free plasminogen. (The heavier the arrows, the greater the effect.)

In 1977, the U.S. Food and Drug Administration (FDA) approved streptokinase therapy for pulmonary embolism and deep venous thrombosis; more recently, the FDA approved streptokinase therapy for acute myocardial infarction.

Urokinase

Urokinase was first isolated in 1947 from human urine[5] and has been synthesized from human fetal kidney using tissue culture techniques since 1967.[17] Urokinase is a two-chain serine protease that causes direct activation of plasminogen and has a half-life of 10–16 minutes[18] (*Figure 1*). Available for investigational use since 1974, it was approved for clinical use in 1977 for acute pulmonary embolism and later for thrombotic occlusion of access shunts, transvascular catheters, or cavity catheters.

Urokinase is not antigenic, and although it frequently causes nausea and vomiting, no clear hypersensitivity reactions have been reported. Despite its higher cost from the pharmacy (i.e., 7–10 times that of streptokinase), a recent cost analysis including administration and complications showed a trivial overall difference in cost.[19] The efficacy of urokinase has been well documented and is considered to equal that of streptokinase.[16]

T-PA

T-PA, another serine protease, was first noted in 1947.[20] It is secreted by vascular endothelium in response to a nearby thrombus. The t-PA protein sequence was recently identified and cloned using recombinant DNA technology.[21] Because of strong binding affinity to fibrin (a cofactor), fibrin-bound plasminogen is converted to plasmin on the clot surface (*Figure 1*). Conversely, fibrin has a low binding affinity to circulating plasminogen.[22] Clot lysis usually occurs promptly without marked decrease of fibrinogen, although more recent studies have shown some fibrinogen depletion. T-PA is metabolized in the liver, where it has a half-life of approximately five minutes.[23]

The FDA recently approved intravenous use of t-PA for acute myocardial infarction. The cost of this therapy is similar to that of urokinase. Efficacy has been shown in numerous studies.[24–28]

Pro-urokinase

Pro-urokinase is a single-chain, naturally occurring precursor to urokinase and is a plasminogen activator. Its therapeutic use remains investigational.[29] This single-chain protein is converted to the active, double-chain urokinase on the clot surface, where it activates plasminogen.[30]

A semi-synthetic investigational agent, anisoylated plasminogen-streptokinase activator complex (APSAC) represents a 1:1 complex of streptokinase with plasminogen. After it binds with fibrin, the complex becomes deacylated, allowing activation of plasminogen.[31–32] Despite the antigenic properties of APSAC, its use in acute myocardial infarction may hold promise because it can be injected intravenously in a single bolus.[33]

MYOCARDIAL INFARCTION

Ever since the use of streptokinase nearly 30 years ago to treat a patient for acute myocardial infarction,[34] the principal aim of thrombolytic therapy has been myocardial salvage. When coronary thrombosis was shown to be the usual cause of acute myocardial infarction, great interest in thrombolytic agents arose.[35]

Classic among modern studies is the Thrombolysis in Acute Myocardial Infarction Trial conducted by the National Heart, Lung and Blood Institute (NHLBI),[25] which involved several phases. This trial documented an almost twofold incidence of angiographically confirmed coronary thrombolysis with t-PA (66%) than with streptokinase therapy (36%). Other studies[24,36,37] cite reperfusion rates as high as 75%–80%. Several recent trials[36,37] have shown significant benefit in anterior myocardial infarction but not in inferior myocardial infarction. Urokinase was not used in these studies, although studies are underway comparing the efficacies of t-PA, streptokinase, and urokinase in acute myocardial infarction.

High rethrombosis and reinfarction rates have motivated researchers recently to undertake studies[38,39] of intravenous administration of t-PA immediately after infarction, followed 48–72 hours later by coronary arteriography and angioplasty. This regimen has shown the best results to date. Further details on use of thrombolysis in acute myocardial infarction are beyond the scope of this article but have been described recently.[40]

VENOUS THROMBOEMBOLISM

Anticoagulants have been used since 1937 to treat venous thromboembolism. Rates of morbidity and mortality are much lower in patients given heparin for pulmonary embolism than in patients receiving no treatment.[41] Anticoagulants, shown to reduce the incidence of recurrent deep venous thrombosis and pulmonary emboli,[42] are now the mainstay of treatment in these disorders despite having no direct effect on dissolution of the thrombus. The role of anticoagulant therapy is to prevent further thrombus growth by allowing the fibrinolytic system to act with subsequent thrombus organization and recanalization of the vessel.[43]

Deep venous thrombsis

In 20%–30% of cases, calf deep venous thrombosis eventually extends into the proximal deep veins[44]; nevertheless, serial noninvasive testing has shown nonpropagating distal thrombosis to have a benign course even when left untreated.[44–47] Anticoagulation is generally recommended for calf thrombi, although it is somewhat controversial; however, treatment with thrombolytic therapy clearly is not indicated.

Proximal venous thrombosis is treated with anticoagulants alone or with thrombolytic therapy followed

TABLE 1
RESULTS OF RANDOMIZED TRIALS OF INTRAVENOUS STREPTOKINASE VERSUS HEPARIN IN TREATMENT OF DEEP VENOUS THROMBOSIS*

Reference	Proportion (%) of patients with thrombolysis†		Relative risk of thrombolysis	Two-tailed P value
	Streptokinase	Heparin		
Robertson et al[50]	7/8 (88)	3/8 (38)	2.3	0.5
Kakkar et al[51]	6/10 (60)	2/10 (20)	3.0	0.08
Tsapogas et al[52]	10/19 (53)	1/15 (7)	7.9	0.005
Porter et al[53]	13/24 (54)	8/26 (31)	1.8	0.10
Elliot et al[54]	17/26 (65)	0/25 (0)	16.0	<0.0001
Pooled result	53/87 (61)	14/84 (17)	3.7	<0.0001

*Adapted from Goldhaber et al.[49]
†Documented venographically.

by anticoagulants. Because thrombosis frequently recurs, surgical thrombectomy is generally not indicated[48]; thrombolytic agents can be used when aggressive therapy is warranted.

Many trials have compared heparin therapy and thrombolytic therapy in the treatment of deep venous thrombosis. A pooled analysis of randomized studies concluded that streptokinase therapy elicits thrombolysis 3.7 times more frequently than does heparin therapy[49] (*Table 1*). Major bleeding occurred 2.9 times more frequently in the patients treated with thrombolysis compared with heparin. Streptokinase therapy elicited venographically documented thrombolysis in 53%–88% of patients as compared with 0%–38% of patients treated with heparin[50–55]; and the highest efficacy for streptokinase therapy occurred in patients who had had symptoms for fewer than seven days and whose therapy continued for more than 48 hours.[53,55–58] One study[53] found no correlation between clinical manifestations and venographically documented improvement. Use of streptokinase to resolve clots holds little promise in patients whose symptoms have lasted longer than seven days.[56]

In randomized trials,[50–54] complications occurred most frequently among patients treated with streptokinase. Three studies[50,53,54] documented major bleeding in 8%–25% of patients given streptokinase and in 0%–12% of patients given heparin alone. No correlation was noted between laboratory parameters monitored and frequency of bleeding after streptokinase administration[56] or, as in a more recent study,[57] after urokinase administration. Bleeding was more often related to total daily dose or to duration of therapy, and hypersensitivity reactions occurred almost exclusively in patients treated with streptokinase.

In a recent study,[19] we compared streptokinase and urokinase therapies in the treatment of deep venous thrombosis. These therapies achieved equal degrees of thrombolysis; however, in the streptokinase group, thrombolysis required twice as much time to occur (58 hours as compared with 26 hours), and major bleeding complications occurred more frequently ($P<0.01$).

Because it remains unclear whether risk of pulmonary embolism is diminished by thrombolytic treatment of deep venous thrombosis, and because standard anticoagulation effectively prevents pulmonary emboli, the goal of thrombolytic therapy is to prevent postphlebitic syndrome. This prevention is possible when venous valvular function is preserved (*Figure 2*). Chronic venous insufficiency causes a significant alteration in lifestyle and, in many patients, a substantial economic burden.[58]

Several smaller trials have evaluated long-term outcome of patients with prior deep venous thrombosis. In 40% of patients treated with streptokinase, venograms repeated after a mean of seven months were normal (in these patients, initial symptoms had lasted fewer than three days), whereas 8% of repeat venograms were normal in patients treated with heparin.[55] In another study,[59] follow-up at a mean of 6.5 years found "normal legs" in 76% and normal venograms in 41% of patients treated with streptokinase; normal legs were seen in 33% and normal venograms in 0% of patients treated with heparin. Severe postphlebitic changes were seen less often in another follow-up clinical evaluation eight to 14 years after treatment with thrombolytic therapy.[60]

Pulmonary embolism

Anticoagulants have proved to be effective in management of patients with suspected or proven pulmonary embolism.[41,61] The mortality rate is reduced to less than 10% in these patients, compared with a 30% mortality rate in untreated patients.[62–64] Demonstrable pulmonary emboli can resolve substantially (and sometimes completely) with heparin therapy alone.[62,65] For patients in whom anticoagulant therapy is contraindicated, inferior vena cava interruption offers equal benefit.[63]

Surgical intervention with pulmonary embolectomy,

with or without cardiopulmonary bypass, has resulted in mortality rates of 23%–100%.[66–68] For patients with massive pulmonary embolism and hypotension unresponsive to therapy, the role of surgical thrombectomy is diminishing because of current success with thrombolytic therapy.[69] General anesthesia may be avoided when transvenous intraluminal catheter embolectomy is done; this technique has had some success in a small number of patients.[70,71]

Thrombolytic therapy for acute pulmonary embolism has been compared with anticoagulants in randomized trials.[62,72,73] The urokinase pulmonary embolism trials (UPET)—or Phase I trial—sponsored by NHLBI randomized 160 patients (who had arteriographically proven pulmonary embolism) to treatment with heparin or urokinase. Patients receiving a 12-hour infusion of urokinase had better resolution of defects as shown by lung scans or pulmonary arteriograms at 24 hours, and hemodynamics were also substantially improved. Although early superior results were seen with thrombolytic therapy, lung scans performed one week to one year later showed that anticoagulants alone produced matching improvement. No difference was seen in frequency of recurrent pulmonary embolism or in mortality rate two weeks after onset of therapy.[62] Although bleeding complications occurred almost twice as frequently in patients treated with urokinase as in patients treated with heparin, bleeding almost always occurred at sites of previous vascular invasion.[62,72–74] Lower mortality rates with urokinase therapy have not been demonstrated.

The Phase II NHLBI-sponsored trial compared 12-hour and 24-hour urokinase therapy and 24-hour administration of streptokinase in 167 patients who had pulmonary embolism. Urokinase given for 12 or 24 hours was approximately equal in efficacy to streptokinase therapy, whereas 24-hour urokinase therapy was superior to 24- hour streptokinase administration according to lung scan findings only. Urokinase seemed to produce quicker resolution in patients who had massive pulmonary embolism. No difference in mortality rate was found between the different groups. Presumably because of fewer procedures, less bleeding was found in the Phase II trial: 16% of patients required one or more transfusions.[16]

Rapid resolution of thrombosis may result in early stabilization of patients who have massive pulmonary embolism (40% or more perfusion deficit). Rates of mortality and long-term morbidity attributed to pulmonary compromise may be decreased in these patients if treated with thrombolytic therapy. Patients chosen from the Phase I and Phase II trials were found to have had improved pulmonary diffusion capacity and higher pulmonary capillary blood volume when assessed at two weeks and at one year after treatment with urokinase or streptokinase.[75] Reports of chronic pulmonary hypertension secondary to pulmonary emboli have been increasing; thrombolytic agents, if used early, may prevent this devastating sequela.[76,77]

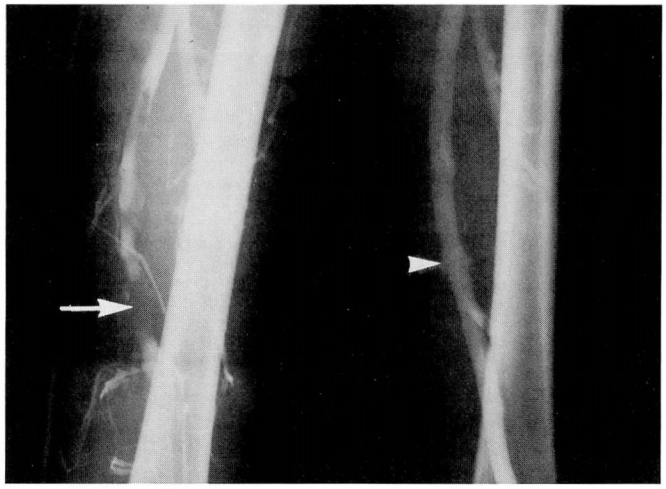

FIGURE 2. Acute superficial venous thrombosis before (left, arrow) and after (right) 48 hours of urokinase infusion. Note excellent preservation of venous valvular structures (arrowhead) after urokinase infusion.

Use of newer thrombolytic agents for treatment of pulmonary embolism is in the early stages of investigation. In a recent trial,[28] wherein 47 patients with pulmonary embolism were given t-PA intravenously over a period of two to six hours, moderate or marked thrombolysis occurred in 83% of the patients and major bleeding occurred in only 4%. The comparative benefit, risks, and optimum regimen of this newer agent in this setting remains to be determined.

SUMMARY

Myocardial infarction

The well-established benefit of thrombolytic agents in the treatment of acute myocardial infarction has resulted in rapidly expanding interest in their use. Trials are underway not only to determine the best thrombolytic regimen but also to establish the best timing of other procedures necessary to maintain or improve myocardial perfusion.

Venous thromboembolism

The optimal therapeutic agent and dosage for treat-

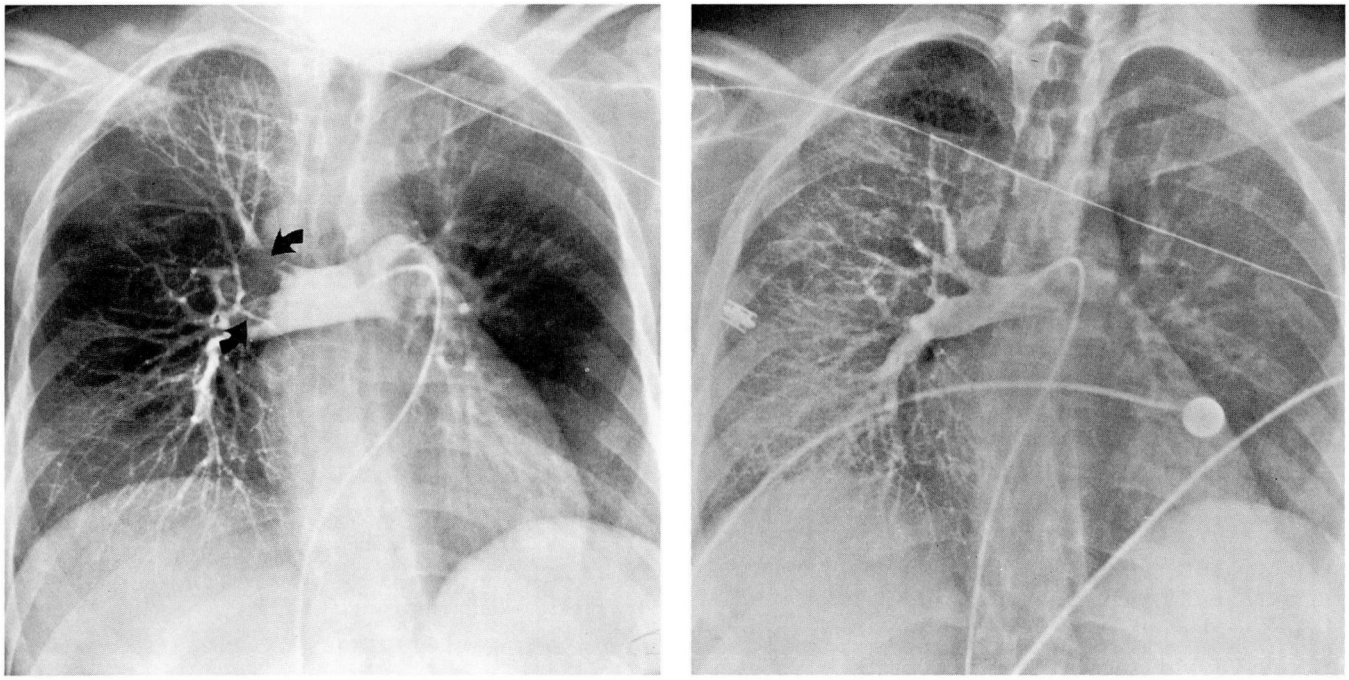

FIGURE 3A. Large thrombus of right main pulmonary artery and its branches (arrow) represent acute pulmonary embolism.
FIGURE 3B. Complete resolution of thrombus 12 hours after urokinase infusion.

ment of deep venous thrombosis and pulmonary embolism remains to be determined. However, a recent analysis of thrombolytic regimens used in treating pulmonary embolism recommended the dosages used in the UPET and USPET studies.[78]

1. Streptokinase was given in a standard regimen of a loading dose of 250,000 IU administered over a 30-minute period, followed by continuous intravenous infusion of 100,000 IU/hr.[79]

2. Urokinase dosage regimens have varied greatly, but the standard regimen consists of a loading dose of 4,400 IU/kg given over a 10-minute period, followed by administration of 4,400 IU/kg/hr. Infusion via pulmonary arteriography catheter does not seem advantageous when compared with intravenous infusion.[80,81] If pulmonary arteriography is done, the catheter is usually left in place to decrease any bleeding from the inguinal puncture site and to enable repeat arteriography after infusion of the thrombolytic agent (*Figure 3*).

Deep venous thrombosis. Data regarding the value of thrombolytic therapy for deep venous thrombosis is less encouraging than for its value in myocardial infarction. Whether preservation of venous valvular function translates into prevention of chronic venous insufficiency—with its costly and debilitating sequelae—remains to be clearly demonstrated.

For deep venous thrombosis, little is currently known about results other than with continuous infusion of the thrombolytic agent. Progress is monitored by using serial daily venography or, alternatively, with noninvasive venous studies (preferably duplex venous imaging). Discontinuation of treatment is recommended when clot lysis is substantial enough to make unlikely the development of chronic venous insufficiency, when no further improvement is noted, or if a serious complication occurs.

Pulmonary embolism. Thrombolytic therapy for pulmonary embolism may be administered continuously by intravenous infusion until clinically significant or complete thrombolysis is shown by serial perfusion lung scans or pulmonary arteriography, until no further improvement is seen or until a serious complication occurs.

In pulmonary embolism, thrombolytic agents can produce rapid improvement or resolution of defects as shown by lung scans or pulmonary angiography. However, much controversy remains concerning selection of patients who will benefit most from this therapy. Patients with massive pulmonary embolism should be treated with thrombolytic therapy as long as no contraindications are present. The role for thrombolytic therapy for submassive pulmonary embolism is unclear at the present time. Because of contraindications, few

patients with acute pulmonary embolism are appropriate candidates for thrombolytic therapy.

In Part 2 of this article, (to be published in a subsequent issue of the *Cleveland Clinic Journal of Medicine*), we will review the use of thrombolytic agents in treating arterial occlusions, arterial venous fistulas and grafts, and stroke. We will attempt to provide a rational dosing scheme and a method for monitoring thrombolytic therapy. Complications of thrombolysis will also be discussed.

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